REMARKS

Claims 1-4, 9-12, and 28-37 are pending in the application. New claims 38-40 have been added. Support for the newly added claims can be found throughout the specification. No new matter has been added.

Allowed Claims

Applicants gratefully acknowledge the Examiner's indication that claims 29, 31, and 37 would be allowed if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Accordingly, Applicants have added new claims 38-40.

Objection to the Specification

The Examiner stated the disclosure failed to comply with 37 C.F.R. § 1.821(d), because the sequences disclosed were not accompanied by SEQ ID Numbers. Appropriate correction has been made to the description, and amended paper and computer readable versions of the Sequence Listing are submitted herewith. A SEQ ID is not included for the "primer" taught at page 30, line 9, due to the fact that one of ordinary skill in the art would recognize that different sequences could be used. No new matter has been added.

Rejection of Claims 1-4, 9-12, 28, 30, and 32-36 under 35 U.S.C. § 103(a)

Claims 1-4, 9-12, 28, 30, and 32-36 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Linsley *et al.* (U.S. Patent 5,521,288), or, in the alternative, over Yu *et al.* (U.S. Patent Pub. 2002/0006403). According to the Examiner, Linsley *et al.* and Yu *et al.* teach methods of treating autoimmune diseases, including type I diabetes, by administering anti-CD28 antibodies. Applicants respectfully traverse this rejection.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* showing of obviousness with respect to the rejected claims. In order to establish a *prima facie* case of obviousness, the Examiner must determine the scope and content of the prior art, ascertain the differences between the claimed invention and the prior art and resolve the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 (1966). Once the

Graham factual inquiries have been resolved, the Examiner must explain why the differences between the cited references and the claims would have been obvious to one of ordinary skill in the art. Fed. Reg. Vol. 72, No. 195, p. 57527. The Supreme Court in *KSR* stressed that "obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR* 127 S.Ct. 1727, 1740 (2007); see also Fed. Reg. Vol. 72, No. 195, p. 57529. "The key to supporting any rejection under 35 U.S.C. §103 is the clear articulation of the reason(s) why the claimed invention would have been obvious." Fed. Reg. Vol. 72, No. 195 at p. 57528.

The Examiner alleges that it was well known in the art at the time of the invention that CD28 is a costimulatory receptor, whose activation by B7-1 and B7-2 ligands contributes to upmodulation of an immune response both *in vitro* and *in vivo*. The Examiner therefore asserts that it would have been obvious to one skilled in the art that blocking the interaction of B7-1 and/or B7-2 with CD28 would result in downmodulation of an immune response.

Applicants respectfully traverse these rejections. Specifically, in the Office Action dated March 8, 2007, the Examiner was of the opinion that Linsley *et al.* explicitly teach that anti-CD28 antibodies can be used to treat insulin-dependent diabetes mellitus (column 36, lines 36-43). Linsley *et al.* disclose that mAB 9.3, an anti-CD28 antibody, is an inhibitor of an *in vitro* immune response that is dependent on the interaction of B7 and CD28. Accordingly, Linsley *et al.* performed *in vitro* experiments in various cell lines. On the basis of these results, Linsley *et al.* merely suggest that inhibition of CD28 with an anti-CD28 antibody may treat various autoimmune disorders. However, the *in vitro* data that Linsley *et al.* provides does not teach or suggest any reasonable likelihood of success *in vivo*. Even Linsley *et al.* disclose that, "[t]he in vivo function of CD28 antigen is not known…" (column 1, lines 55-59). In short, it would not have been obvious to one skilled in the art and there would have been no reasonable expectation of success, based on the teachings of Linsley *et al.*, to use an anti-CD28 antibody to downmodulate an autoimmune response in a subject having diabetes mellitus.

The Examiner is also of the opinion that Yu *et al.*, in Example 3 (page 22) provides evidence that anti-CD28 antibody is effective in downmodulating an immune response *in vivo*. The Examiner asserts, in the Office Action dated March 8, 2007, that "Yu *et al.* teach that blocking antibodies can be used to treat autoimmune diseases, such as diabetes mellitus."

Furthermore, according to the Examiner, "[t]he skilled artisan had a reasonable expectation of success, at least in view of the *in vivo* data of Yu *et al.*"

Applicants traverse the rejection. As set forth above, the claims of the present invention are drawn to methods of downmodulating an autoimmune response, ongoing immune response, or CD28-mediated interaction in a subject having type I diabetes, via administration of anti-CD28 blocking antibodies.

In contrast, Yu *et al.* disclose that an anti-CD28 antibody prevents graft-versus-host disease (GVHD) in an animal (mouse) model. While Yu *et al.* generally suggests that anti-CD28 antibodies may be used to treat other immune related disorders, it merely names diabetes in a list of other unrelated diseases (paragraphs 0013, 0020, and 0039 and Table 1) and does not provide an enabling disclosure for the treatment of diabetes. One of skill in the art would appreciate that there would be no basis to extrapolate results from GVHD to an autoimmune disease, let alone, type I diabetes, as currently claimed. GVHD is not an autoimmune disease. The pathologic state in autoimmune diseases, such as Hashimoto thyroiditis and Graves disease, involves antibodies that are directed and targeted to "self" or autoimmunity is the feature. On the other hand, in GVHD, immunologically competent cells or their precursors are transplanted into immunologically crippled recipients. Donor (graft) T-cells recognize the recipient's (host's) HLA antigens as foreign and react against them. Thus, it would not have been obvious to one skilled in the art to use the *non-autoimmunologic* data from Yu *et al.* to downmodulate an *autoimmune* response as set forth in the claims.

As previously discussed, in the response to the Office Action dated March 8, 2007, Bolton & Bradley (*Am. J. Transplant.* 2006, 6: 857-858; previously submitted as Appendix B), discuss treatments effective for certain immune-related disorders that may be ineffective for others. In the Editorial, the authors discuss the failure of treatment with CTLA4-Ig to inhibit the development of disease in any of three experimental models of diabetes. In one model, treatment with CTLA4-Ig accelerated the onset of the disease. This is despite the fact that "CTLA4-Ig is effective in preventing pathology in several other models of autoimmune disease." The authors state, "[i]nterestingly, although anti-CD86 prevents disease in the NOD mouse, anti-CD80 blockade alone accelerates the development of diabetes." These results show the inherent inaccuracy in extrapolating treatment efficacy even within a disease. The inaccuracy in extrapolating between disease classes (*i.e.,* GVHD to autoimmune), as Bolton and Bradley

suggest, is expected to be even greater. In light of Bolton and Bradley, the disclosure of Yu *et al.* does not provide a reasonable expectation of success in downmodulating an immune response in a subject with type I diabetes, as claimed in the instant application. Even if one were to combine the general suggestion of treating diabetes made by Yu *et al.*, with the data pertaining to GVHD, it would not be obvious to one skilled in the art to practice the claimed invention. In view of the foregoing, Applicants respectfully request withdrawal of the claim rejections under 35 U.S.C. 103(a).

CONCLUSION

In view of the foregoing remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-832-1000. The Commissioner is authorized to charge any underpayments, or to credit any overpayment, to Deposit Account No. **06-1448, reference WYS-007.01.**

Respectfully submitted,
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